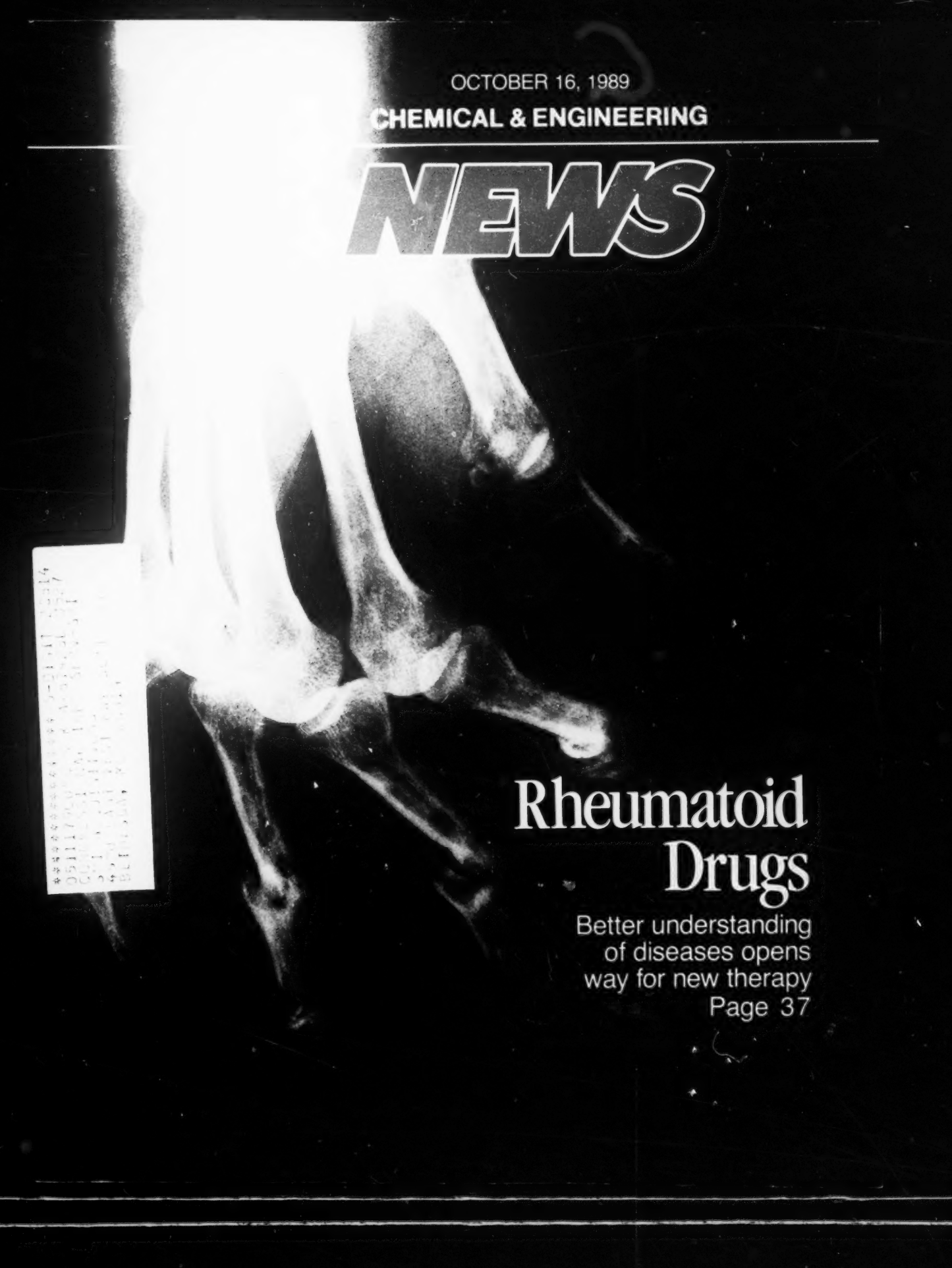
OCTOBER 16, 1989
CHEMICAL & ENGINEERING
NEWS



Rheumatoid Drugs

Better understanding of diseases opens way for new therapy

Page 37

CHEMICAL & ENGINEERING NEWS

Volume 67, Number 42
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OCTOBER 16, 1989

News of the Week

■ **For work in molecular biology, two U.S. scientists win Nobel Prize in Chemistry, and two others receive the medicine or physiology prize; two U.S. scientists and a West German earn physics prize for contributions to atomic precision spectroscopy.** **Page 6**

■ **NSF to require that research proposals include a statement on how a project will contribute to the training of future scientists and engineers.** **Page 7**

■ **Vietnamese scientists seeking to build ties with U.S. scientists.** **Page 8**

■ **ICI sells over-the-counter drug business to Johnson & Johnson-Merck Consumer Pharmaceuticals, shifts focus of its U.S. drug business.** **Page 8**

Business

Chemical industry is becoming more global, but still has long way to go, executives conclude at Society of Chemical Industry meeting. **Page 15**

Government

Chemists are big part of FDA's new drug approval process; National Research Council calls for major boost in ag research funding; NIH and industry examine pitfalls to be avoided in collaborative efforts. **Page 19**

Science/Technology

Iowa tries to attract biotech firms using showcase presentation of university facilities and research; two new fibers challenge insulating properties of duck down; Wayne State University researchers reproduce evidence of superconductivity above 200 K; new way to synthesize high-tech crystalline solids; Japanese exhibit aims at improving public's image of chemistry. **Page 24**

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Gloomy assessment of U.S. science education was heard by academic/industrial group attending the annual meeting of the Council for Chemical Research. **Page 33**

ACS News

The society's Campaign for Chemistry receives $2.5 million donation from Mildred and Donald Othmer. **Page 72**

Awards

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Cover: X-ray of arthritic hand. Photo courtesy of Arthritis Foundation

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Product Report

Understanding of the immune system and progress in the methods of biotechnology have brought chemists to the threshold of a new generation of compounds to treat rheumatoid disease. **Page 37**

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LETTERS

Origin of inventions

SIR: I agree completely with Charles Milliren (C&EN, Aug. 28, page 2) that present emphasis on the management track for young chemists and engineers denies them the intensive exposure and incubation in technology that they must have before they can make patentable inventions.

Milliren's letter was far too polite. During my career, management was ignorant technically, but willing to consider a development program, if properly presented, that might take as long as five years. The new graduate business school managers are taught to look out first for themselves, since only what is good for them is good for the corporation. What is good for them is this year's bottom line, and anything else be damned. They suffer from the delusion that inventions originate not in trained, experienced minds, but in a computer.

Only a terrible depression will rid us of these incompetents and bring us back to hard work and common sense.

George Karnofsky
Emeritus member
Pittsburgh, Pa.

Strategic Defense Initiative

SIR: I have a problem supporting the so-called Strategic Defense Initiative, or "Star Wars." Assume that two or more completely effective systems are developed, deployed, and forced into use by a hostile globe-traversing launch. Assume that all offensive missiles are successfully destroyed prior to reaching their targets. Would not some of them be hit by satellite-based defensive missiles during their rising trajectory and thus in some cases over their home territory? Would not some be destroyed during their high-altitude passage? And would not some finally be destroyed in the atmosphere close to their targets? Do not all these missiles, offensive and defensive both, contain fissionable and fusionable materials as well as high explosives and other forms of high energy? Would not mankind thus then have created an immense radioactive globe-girdling cloud of lethal fallout?

Perhaps these questions are too simplistic. However, I raise them for examination by our scientific community. Years ago I came to the conclusion that the weapons we used to end World War II should be the last mankind ever employs in anger.

What, then, can we do to continue our presently promising march for world peace? There are many definitely encouraging signs of progress. For instance, we are talking much more than we are fighting. This may be frustrating but it is rarely fatal.

William S. Hutchinson Jr.
Former Commander,
Joint Task Force Eight, Nuclear Testing

Preserve the name of chemists

SIR: The grievance regarding taxed meeting expenses by Raymond B. Seymour (C&EN, July 24, page 3) prompted me to write this letter.

For centuries, the reputation and salary compensation of chemists has always been beneath engineers, architects, and medical doctors, although chemistry is the oldest profession. This makes one wonder why, and I might have answers to this puzzle.

First, as a private consultant, I frequently have to compete with university professors and staff members for consulting and expert witness services. My fee is higher simply because I do not have a regular paycheck as they have, and, naturally, they will be retained as a consultant. This trend will force professional consulting chemists to get paid like a technician, and, thus, chemists work like slaves compared with other professionals.

Second, other degreed professionals, except chemists, have something to look forward to. For example, engineers want to acquire the title of professional engineer, accountants the title of Certified Public Accountant, and architects American Institute of Architects licensure. It is quite important in court that a chemist have certain recognition like the title of certified professional chemist. I sure hope that all chemists try to preserve the name of chemists.

Michael K. W. Li
President, Industrial Analytical Laboratory
Honolulu

Mousy odor of acetamide

SIR: For well over a century, acetamide has been described as associated with the odor of mice. Many of the authorities ascribe the mousy aroma to "an unknown impurity" and reassure the reader that pure acetamide without odor exists. I have prepared acetamide that remained free of mousy odor for several days. Do any of your readers know what impurities cause the mousy odor?

Frank Wagner
Corpus Christi, Tex.

Chemical Company Execs Chart Progress Toward Global Industry

Consensus at Society of Chemical Industry meeting is that industry still has long way to go; more restructuring, transnational mergers needed

Patricia L. Layman, C&EN London

Earlier this month in Venice, the chemical industry's top executives from Western Europe, plus a number of their counterparts from North America and Japan, compared notes and swapped information on the structural trends shaping an ever more global industry. This annual European meeting of the London-based Society of Chemical Industry—the continent's counterpart to the annual meeting of the Chemical Manufacturers Association at White Sulphur Springs—indicated that there is still work to be done within Western Europe to promote a transnational "European" chemical industry, rather than fragmented, smaller national industries.

How that work is accomplished will go a long way toward securing the place of the chemical industry in Europe in the international scene, where cross-cultural differences complicate the way to solving its problems. The problems are global: economic forces, environmental regulations and regulatory pressures, trade balances.

Moreover, an additional complication faces the chemical industry—probably the strongest manufacturing industry in Western Europe. How will it operate in the single internal market due to be in place by the end of 1992 in the European Community? Restructuring is one response. During the past year, for example, there have been several major signs of this activity progressing in Western Europe: the formation of the Italian chemical group, Enimont, for example, and the rumblings of restructuring ahead for the French chemical industry.

Popoff: growth is crucial question

In part, suggested Lorenzo A. Necci, chairman and chief executive officer of Enimont, the ramifications of the formation of a single internal market have made companies aware of the need to restructure and regroup forces within Europe, before tackling the world. "Although some weaker players have quit the game," he said, "we still have the remnants of the idea of petrochemicals as a national strategy." However, he added, "the fortress idea, with countries building walls around their chemical industry, has been a complete failure."

"If the idea of the multinational originated in the U.S.," he said, "I think that Europe is the source of the emerging transnational corporation. In fact, the engine of European integration is being powered by industry, and the chemical sector is playing a leading role."

But, Necci was asked, is not the creation earlier this year of Enimont from an amalgamation of EniChem and many of the chemical operations of Montedison—a creation he described as a "child of the market's needs and a defeat of the national mentality"—an indication that national thinking is still paramount? He acknowledged the apparent contradiction, but added, "First, you must clean up your house, to then deal with more strength and authority outside. Enimont is a beginning, in cooperation with Europe."

Nonetheless, as Robert Malpas, outgoing chairman of these autumn conferences and recently retired chairman of U.K.-based BP Chemicals, pointed out in his opening remarks, it is still far easier for a West European company to make a major merger or acquisition in the U.S. than in another country in Europe.

"There needs to be more transnational ownership; there needs to be more ease in transnational mergers and acquisitions," he argued. Indeed, this is an area in which companies, and commissioners within

Major transnational deals lagged in Western Europe in 1988

Mergers/acquisitions greater than $100 million	Value of deals, $ billions	Number of deals
Europe, within one country	$ 59.6	100
Transatlantic, Europe/North America	52.6	101
Europe, cross-border	13.2	24
Europe/Asia	8.8	15
TOTAL EUROPEAN	$134.2	240
TOTAL U.S.	$202.5	323

Source: First Boston

the EC are still feeling their way toward encouraging world-scale competitive forces.

And, perhaps less obviously, one arena for such mergers and acquisitions could be Japan, suggested Shigekuni Kawamura, president of Tokyo-based Dainippon Ink & Chemicals.

Some Japanese chemical companies are beginning to make acquisitions outside their own country, although slowly. "We have little experience in selling outside Japan, little experience in production [outside Japan]. We would probably have to do joint ventures, pooling research, or have joint investment, but little in the way of outright takeovers," he said. "A hostile takeover would not work—the acquisition should be on a friendly basis, with negotiations." Those takeovers that do occur—such as that of Reichhold Chemicals and Sun Chemical by Dainippon—come about only when there have been long-standing relationships or working agreements. "We wouldn't buy unless we were sure we could find the right people to manage a U.S. or European company."

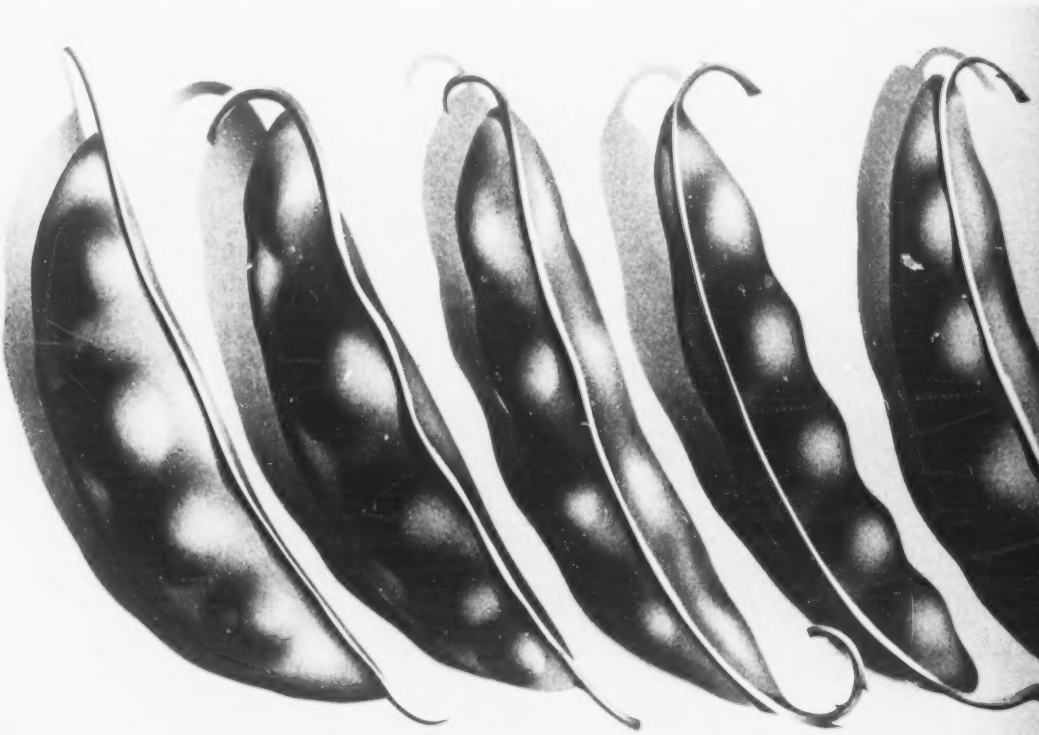
Moreover, Kawamura added, "it is easier for a non-Japanese company to buy a Japanese company: It is in your culture. For a Japanese company to buy a Japanese company is very difficult, because it is not in our culture."

Frank Popoff, president and chief executive officer of Dow Chemical, noted that "all manner of rationalizations, restructurings, mergers, acquisitions, joint ventures, and strategic alliances have had global reach and penetration as paramount motives. Counterproductive economic nationalism has been identified for what it is—an unsuccessful short-term defense against the power of global commerce."

A crucial question for the industry to ask, on a worldwide basis, he suggested, is the simple one: Is the chemical industry still a growth industry? Will new uses for polymers and plastics grow faster than environmentally driven reductions in demand? The same question, he added, also could be asked of chlorinated products, organic solvents, pesticides, and a variety of other chemicals. Will new applications grow fast enough to counterbalance the cuts in consumption that environmental pressures force?

"I suspect that few producers are discounting plastics growth by recycling rates and disuse initiatives," Popoff said.

As pressures against the chemical industry become more international, the need for industry to reflect the same international counterbalance becomes that much more important. At present, strong nationalistic forces still constrain corporate structure and ownership in the Western European countries. However, if further restructuring is to take place, legislation concerning



corporate structure and ownership will have to change significantly and quickly.

That, at least, was the prediction of Lord Francis A. Cockfield, a consultant on European affairs for Peat, Marwick McLintock, a London-based consulting firm. Cockfield, a vice president of the European Commission from 1985 to 1988, was the driving force and architect of the plan to bring about the single internal market.

According to Cockfield, the way the EC is developing—not only up to 1992, but beyond—"is of immense importance to industry and not least to the chemical industry because of its long tradition of international operation." This concern, he suggested, needs to be reflected at two levels: an industrywide level and an individual company level.

For the industry as a whole, he said, it is essential to watch, to understand, and, where necessary, to influence developments by contacts with the commission, with the European Parliament, and with the governments of the member states. This means, he added, with the commissioners directly involved in the pertinent areas and with the permanent employees in the bureaucracy of the commission.

For the individual company, no matter whether it is based in Europe, the U.S., or elsewhere, the question is one of developing a strategy to meet the opportunities and challenges not only of the internal market but also of the developments that will follow, Cockfield said. This, in turn, requires an in-depth knowledge of the community, of its policies, of community law, and particularly how that law is likely to develop.

One thing helping industry, he added, is the openness in the way the European Commission operates. In the development of the single internal market, for example, "at every stage, you could see the policy, and the way it was developing. There is not the secrecy of some member states' governments toward, for example, parliaments."

"1992 will inevitably require a restructuring of European industry," he pointed out. "We should take a positive attitude to measures that will assist with that."

How those measures develop will, of course, be crucial. But they cannot be tailored to cater to mere slogans or political posturing, Cockfield argued. "Simplistic beliefs in deregulation and free enterprise, for example, can lead to serious error. Excessive regulation may be bad, but equally excessive deregulation may be equally bad."

One of the most important things, he concluded, is the willingness of industry to temporarily assign "some of its best people to serve on committees to formulate standards, regulations, and so on. Ensure that your experts are there, when the spadework is being done." □

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Photo by Janet L. Stevenson-Kruzel

Better Understanding of Arthritis Leading to New Drugs To Treat It

Stephen C. Stinson,
C&EN Northeast News Bureau

Understanding of the immune system and progress in the methods of biotechnology have brought medicinal chemists to the threshold of a new generation of compounds to treat rheumatoid disease. As a product category, rheumatoid drugs are thus poised to generate increased sales and earnings for their developers owing to introduction of more effective, patent-protected biological and synthetic organic agents.

But drug companies face a treacherously shifting marketing climate today and into the 1990s in so-called nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs are the most numerous, most widely used, and best selling of the category.

In one development, patents are expiring one after another, leading to competition of new generic versions against established branded drugs. Although doctors' and patients' confidences may have been shaken by recent reports of corruption and sloppy record keeping in tests and approvals of some generic drugs, no NSAID has been implicated.

In another development, the Food & Drug Administration has approved one popular NSAID, ibuprofen, to join aspirin in lower priced, over-the-counter marketing. The number of such OTC approvals is likely to increase in coming years. Though FDA will never approve OTC labels that claim effectiveness against such serious diseases as arthritis, doctors will surely guide their patients to them as first-line therapy as they appear together with instructions about how many pills comprise an anti-inflammatory dose.

The appearance of new NSAIDs and other categories of rheumatoid drugs makes it impossible to predict the marketing fortunes of older, potent, second-line drugs such as oral and injectable steroids, gold salts, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine, methotrexate, and cyclophosphamide.

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Rheumatoid diseases and drugs used to treat them

Rheumatoid diseases have a common feature in which the body mounts an immunologic attack against its own tissue. Examples are rheumatoid arthritis, systemic lupus erythematosus, Sjögren (SHOW-gren) syndrome, scleroderma, polymyositis, and dermatomyositis. They are also called collagen-vascular diseases and immune diseases of connective tissue.

But rheumatoid diseases are hard to define and difficult to diagnose. Doctors often simply have to "know them when they see them." Fifty years ago, physicians recognized only a handful. Today, they distinguish among more than 100 rheumatoid syndromes of various tissues. As the number grows and research continues, understanding and treatment will surely improve.

In addition to rheumatoid diseases, this report also covers osteoarthritis. Though not rheumatoid in nature, osteoarthritis can be as devastating as rheumatoid arthritis, and they share some features of pharmacotherapy.

Pain and tissue destruction of rheumatoid diseases result both from acute inflammation and from some unknown "rheumatoid process," which may be more than autoimmunologic attack. Thus there are two basic classes of drugs to treat them.

Nonsteroidal anti-inflammatory drugs (NSAIDs) alleviate pain, swelling, and tissue destruction of inflammation. NSAIDs take their name from oral steroids once favored to treat arthritis. As steroids fell from favor for this use, doctors turned to nonsteroidal drugs. The simplest NSAID is aspirin, though others include ibuprofen, naproxen, diclofenac, piroxicam, and sulindac.

The second class of "disease-modifying drugs" is a baffling collection of agents, some first used to treat other diseases, that seem to arrest the rheumatoid process in unknown ways. Examples are gold salts, penicillamine, hydroxychloroquine (an antimalarial), azathioprine (an immunosuppressant), and methotrexate and cyclophosphamide (anticancer drugs).

Many of these were developed to treat other diseases, and the reasons that they work against rheumatoid diseases are often unknown.

One analyst who has studied the marketing climate for prescription NSAIDs is Karl L. Habermas, of the investment research and management firm Sanford C. Bernstein & Co., New York City. Habermas estimates sales of $1.5 billion in 1989, growing at 11% per year to $2.3 billion in 1993.

To reach these figures, Habermas assumes that FDA will approve five new compounds during the period to join the 13 now available. At first sight, this total of 18 drugs of the same class may seem excessive, but there is a valid place for each in medical practice.

This is because each patient is an individual. Rheumatoid disease or osteoarthritis can be different in each person, and patients vary in susceptibility to such side effects as gastrointestinal upset and ulcers and kidney damage.

Thus doctors usually try high doses of aspirin first. If this is ineffective or not tolerated, the next step is a tour through the whole class of NSAIDs until an effective one is found. But this situation also means that the success of any new NSAID can depend not only on effectiveness and tolerability but also on the marketing prowess of its developer.

To Habermas, the most spectacular launch in recent years was that of Ciba-Geigy's Voltaren brand of diclofenac in 1988. Numbers of prescriptions peaked five months after introduction, which is very fast growth. Doctors will write 8.6 million prescriptions for it in 1989, Habermas says, which is 11.8% of the total and represents a huge success.

Among factors that Habermas cites that led to this success was mobilization of combined sales forces of both Ciba Pharmaceutical Co., Summit, N.J., and Geigy Pharmaceuticals, Ardsley, N.Y., with Voltaren as their number one priority. In addition, the company sponsored scholarly symposia and lectures about rheumatology, including papers on diclofenac, for two years before FDA approval. And the com-

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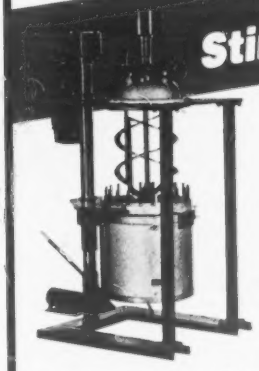

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Arthritis Foundation photo

Lupus patients often develop cheek rash that confers wolflike appearance

pany placed advertising directed at consumers that included retired New York Yankees outfielder Mickey Mantle endorsing the drug.

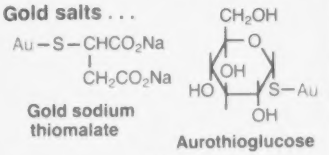
Almost as successful was Upjohn Co.'s launch of Ansaid brand of flurbiprofen last January. Doctors will write 2.3 million prescriptions for this agent of the Kalamazoo, Mich., firm in 1989, Habermas estimates, which is 3.2% of the total.

The Upjohn sales force had to divide efforts among several products, he says, but the company is apparently successful in persuading doctors that Ansaid is a "new Motrin." Upjohn very successfully launched Motrin brand of ibuprofen 15 years ago on the strength of its low incidence of side effects. And Upjohn has agreed with Rorer Pharmaceuticals, Fort Washington, Pa., to market Ansaid jointly.

The next introduction to watch will be that of Relifex brand of nabumetone by SmithKline Beecham, Habermas says. FDA may approve it this year. The marketing effort will be a test of the new company formed by merger of Smith-

Disease-modifying drugs

Gold salts . . .



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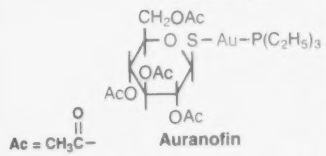
Aurothioglucose



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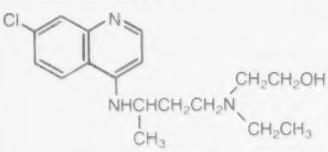
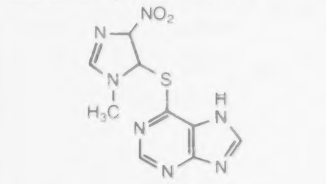


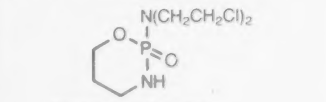
Hydroxychloroquine

Immunosuppressants . . .



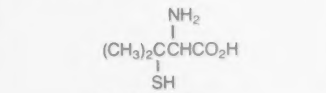
Azathioprine

Anticancer agents . . .



Cyclophosphamide

Others . . .



Penicillamine

Kline Beckman Corp., Philadelphia, and Beecham Group, London, last July.

Meanwhile on the over-the-counter front, Habermas predicts that Syntex Laboratories, Palo Alto, Calif., will soon apply for OTC approval of naproxen. Also, the newly founded joint venture Johnson & Johnson • Merck Consumer Pharmaceuticals Co. may decide to market OTC versions of Merck's diflunesal, indomethacin, and/or sulindac.

The NSAIDs themselves cata-

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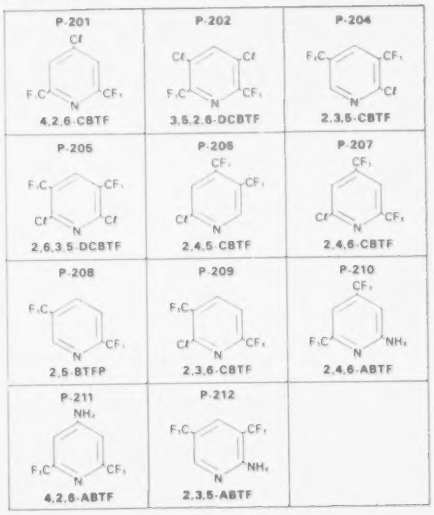

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CIRCLE 31 ON READER SERVICE CARD

pulted into prominence 20 years ago as a result of a hypothesis by medicinal chemist John R. Vane, now at Burroughs Wellcome in England. Vane suggested that aspirin reduced fever, swelling, and pain by inhibiting an enzyme then called prostaglandin synthetase.

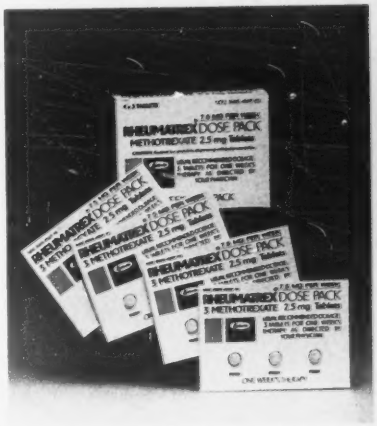
Such symptoms are caused in part by excess biosynthesis of prostaglandins. Prostaglandins are a series of about 20 oxygenated, unsaturated compounds with a 7-(2-octylcyclopentyl)heptanoic acid skeleton.

Synthesized and almost instantly degraded in every body tissue, prostaglandins are extremely potent regulators of a sweeping range of normal functions, including blood pressure and flow, blood platelet aggregation, labor in childbirth, and gastric acid secretion, in addition to pathological pain, fever, and inflammation. Vane's theory proved correct, and he shared the 1982 Nobel Prize in Physiology or Medicine with Sune Bergström and Bengt I. Samuelsson, of Karolinska Institute, Stockholm, who had isolated and studied a wide variety of prostaglandins and related compounds.

It is now known that the cascade of reactions that leads to biosynthesis of prostaglandins and many other compound types begins with liberation of such polyunsaturated fatty acids as arachidonic acid from disrupted membrane lipids, catalyzed by phospholipase A_2.

Among reactions that can occur next, cyclooxygenase catalyzes addition of molecular oxygen across conjugated double bonds to form cyclic prostaglandin endoperoxides such as prostaglandin G_2 (PGG_2). This can be converted to the endoperoxide PGH_2, which in turn leads to mediators of inflammation like PGE_2 and $PGF_{2\alpha}$.

Most NSAIDs known to date are inhibitors of cyclooxygenase. But individual NSAIDs differ in their acidity and ability to cross certain membrane lipid barriers. Thus an agent that works in one patient may be ineffective in another. And shutting down cyclooxygenase in one person's inflamed joint may or may not affect prostaglandin biosynthesis in other tissues.



Lederle packages potent methotrexate for unusual one-day-a-week therapy

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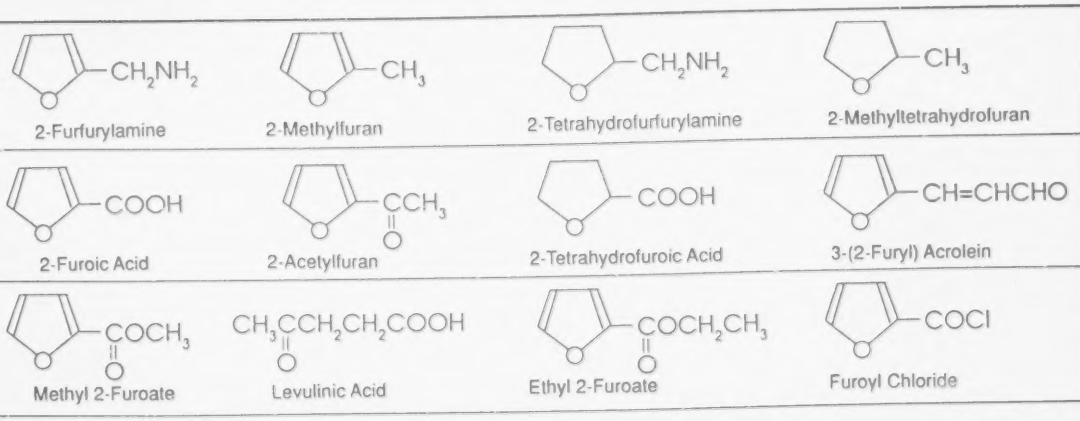

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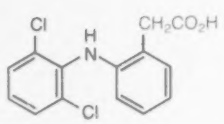
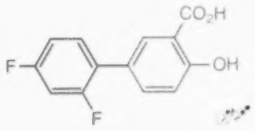
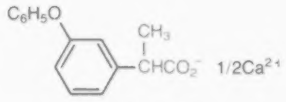
Individuality of patients and disease states requires a variety of anti-inflammatory drugs



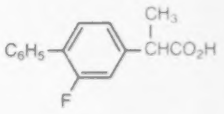
Diclofenac



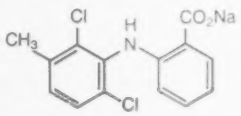
Diflunisal



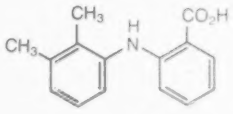
Fenoprofen calcium



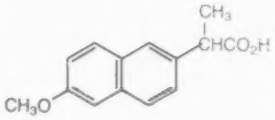
Flurbiprofen



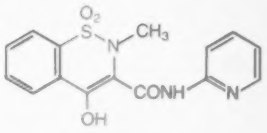
Meclofenamate sodium



Mefenamic acid



Naproxen



Piroxicam

Note: Groups of atoms in color are those that make each compound a member of its class.

prostaglandins suppress excessive gastric acid secretion and help maintain adequate blood flow in and sodium excretion from kidneys. If an NSAID also stops prostaglandin biosynthesis in stomach lining, gastric upset, bleeding, and/or ulceration may result. Ulceration may be insidious, remaining without symptoms until far advanced. And gastrointestinal hemorrhaging can cause death in the elderly.

Stoppage of prostaglandin biosynthesis in kidneys can lead to damage there or can accelerate damage

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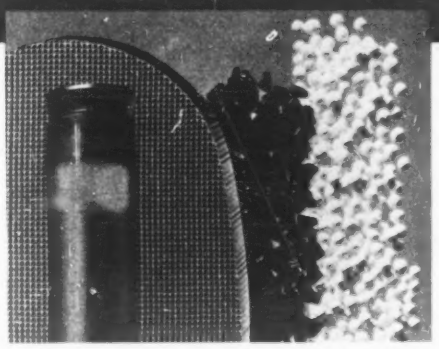

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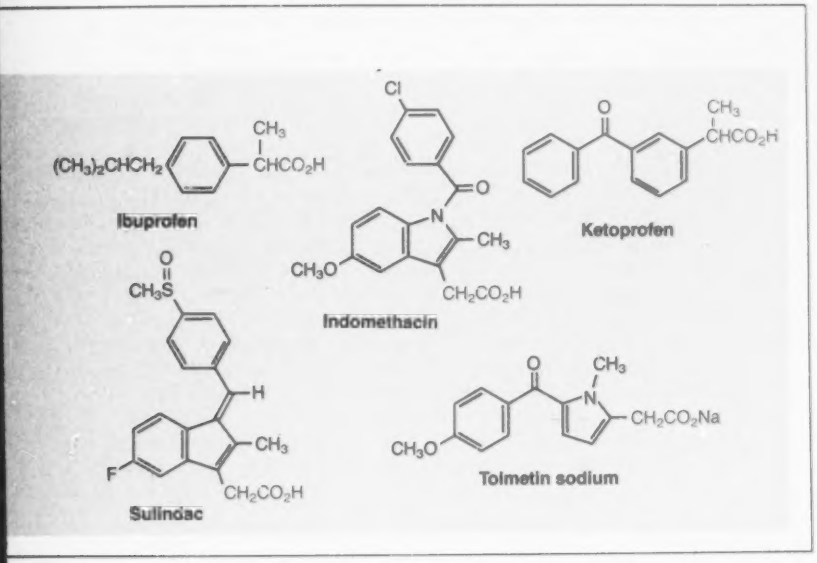
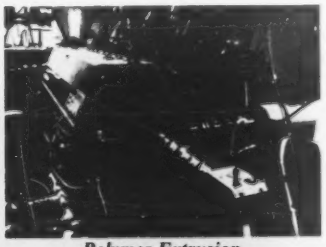


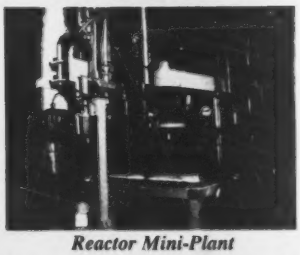
in kidneys that already are impaired. One rheumatoid disease in particular, systemic lupus erythematosus, often includes both an autoimmune attack on kidney connective tissue and arthritis. Thus NSAIDs must be prescribed cautiously for lupus patients.

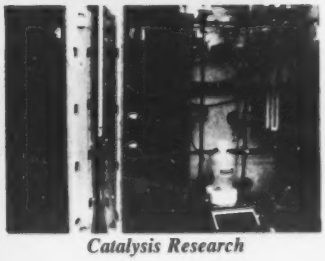
It is to prevent gastrointestinal side effects of NSAIDs that G. D. Searle & Co., Skokie, Ill., got FDA approval to market Cytotec brand of misoprostol. The compound is a 16-hydroxy-16-methyl analog of prostaglandin E_1, but lacks the hydroxyl of PGE_1 at C-15. The compound is absorbed into the bloodstream, from where it apparently replaces the prostaglandin in stomach tissue whose biosynthesis NSAIDs inhibit. Patients take a 200-μg tablet with each meal and at bedtime.

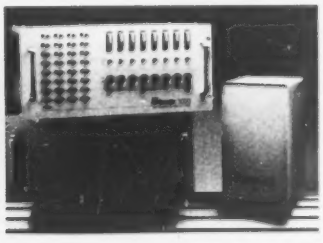
One side effect of Cytotec is bleeding in 40% of pregnant women and miscarriage in some. This is because one of the many normal functions of prostaglandins is to help begin labor at term. Thus Cytotec is contraindicated in pregnant women.

Because of side effects associated with blocking cyclooxygenase, and because prostaglandins are only a few mediators of the complex process of inflammation, medicinal chemists also have explored blocking 5-lipoxygenase. This enzyme also catalyzes reaction of polyunsaturated fatty acids with oxygen, but, in the case of arachidonic acid,


Polymer Extrusion


Reactor Mini-Plant


Catalysis Research



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CIRCLE 15 ON READER SERVICE CARD

to 5-hydroperoxyeicosatetraenoic acid. This compound is converted successively to five mediators of inflammation called leukotrienes A_4 through E_4.

It is against this backdrop that industry observers are watching the progress of tenidap through the approval process. Discovered in the research laboratories of Pfizer in Groton, Conn., the compound has entered Phase III testing (extensive clinical tests in humans). Bernstein's Habermas predicts approval may come between 1993 and 1995, and he has not included it in his market projections.

Tenidap appears to lower production of four different mediators of acute inflammation and perhaps of the enigmatic rheumatoid process itself. These are prostaglandins, leukotrienes, interleukin-1, and C-reactive protein. The six known interleukins are polypeptides secreted by various blood cell types that stimulate one another and cells of other tissues to mount the whole panoply of events of inflammation and destruction that comprises the immune response to antigens. C-reactive protein is one of the so-called acute phase proteins synthesized in the liver during flares of rheumatoid disease. Tenidap's ability to affect four markers of disease makes it the first of a new generation of therapy.

But for all the promise of tenidap, Michael J. Berendt of Pfizer almost takes it all away again as he cautions against reading too much into the evidence. Berendt, who directs Pfizer's department of immunology and infectious diseases at Groton, points out that these findings are only preliminary in an unfinished study in a small number of patients.

Tenidap almost certainly inhibits cyclooxygenase and therefore biosynthesis of prostaglandins in humans. It also blocks 5-lipoxygenase in vitro and decreases leukotriene activity in humans. But actual effect on 5-lipoxygenase in humans is unproven. And knowledge of leukotrienes is so sparse that it is unknown whether suppression of their biosynthesis will benefit rheumatoid patients.

The Pfizer agent seems to decrease concentrations of interleukin-1 in blood of a small number of rheumatoid arthritis patients. In these patients, the amount of messenger ribonucleic acid (mRNA) coding for interleukin-1 seems unaffected. Bererndt suggests that tenidap may affect processing of a 33,000-dalton precursor to the 17,000-dalton interleukin.

As for tenidap's suppression of C-reactive protein, it's not known whether this happens at the level of biosynthesis or whether it results from decreases in interleukin-1. The significance of C-reactive protein also is at question. It may cause some destructive effects of rheumatic disease, or it may simply be a parallel but harmless artifact.

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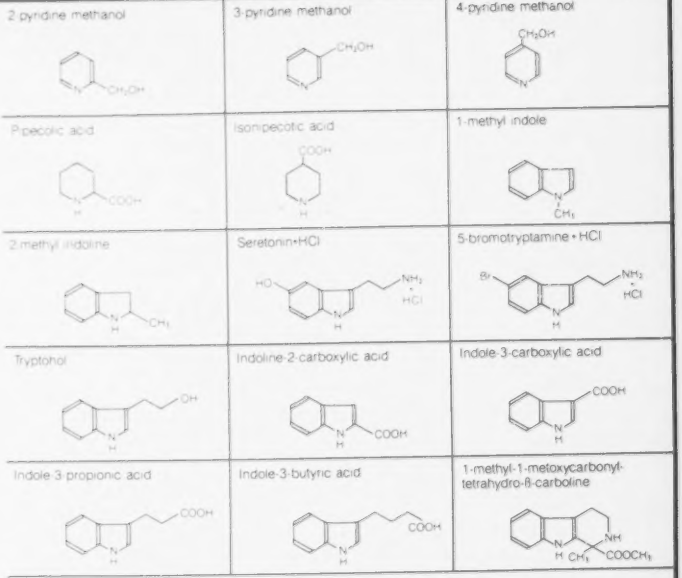

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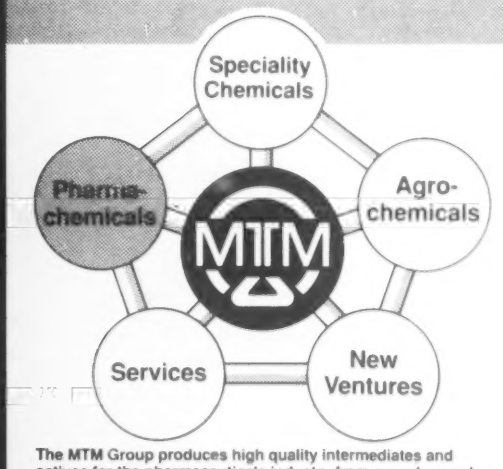
4-Chlorobenzophenone
Cinnamyl Chloride
2, 6-Dimethoxybenzoic Acid
2, 6-Dimethoxybenzoyl Chloride
Dimethylcyanoiminodithio carbonate
Dimethylamine HCl
2-Furoic Acid
2-Furoyl Chloride
(2-Furylacrolein)
1-methyl-6-aminouracil
2-methylbenzophenone
3-methylbenzophenone
4-methylbenzophenone
Methoxyamine HCl (30% solutions, - crystalline solid)
p-methoxybenzyl chloride
2-Methoxy Napthelene (- derivatives)
o-Nitro Benzaldehyde
Potassium Acetate (Solution)
Phenoxy Acetyl Chloride
Phenyl Acetyl Chloride
Theobromine
Thienyl-2-acetyl Chloride
Thiophene-2-aldehyde
Thiophene-2-carboxylic acid
Thiophene-2-carbonyl chloride
2-Thienyl acetic acid
2-Thienyl Glyoxylic (+ esters)



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CIRCLE 35 ON READER SERVICE CARD

Sales of many nonsteroidal anti-inflammatories will fall

Drug (source)	Sales, $ million 1989	Sales, $ million 1993	Average annual change, %
Naproxen (Syntex)	$ 370	$ 520	6%
Diclofenac (Ciba-Geigy)	270	440	47
Piroxicam (Pfizer)	248	235	−3
Sulindac (Merck)	170	105	−11
Flurbiprofen (Upjohn)	78	220	30
Ketoprofen (Wyeth)	55	80	8
Ibuprofen (Upjohn)	50	20	−24
Tolmetin (McNeil)	48	63	3
Ibuprofen (generic)	47	52	4
Fenoprofen (Distra/Lilly)	29	12	−27
Indomethacin (Merck)	29	12	−21
Indomethacin SR (Merck)	23	14	−17
Meclofenamate (Parke-Davis)	19	10	−17
Auranofin (SmithKline Beecham)	17	29	17
Indomethacin (generic)	17	13	−6
Ibuprofen (Boots)	9	5	−19
Nabumetone (SmithKline Beecham)[a]	7	130	b
Etodolac (Ayerst)[a]	6	85	b
Sulindac (generic)	c	40	b
Pirazolac (Berlex)	c	5	b
Oxaprozin (Searle)	c	42	b
Carprofen (Roche)	c	20	b
Fenbufen (Lederle)	c	20	b
Tenoxicam (Marion)	c	5	b
Piroxicam (generic)	c	45	b
Others	49	72	14
TOTAL	**$1541**	**$2294**	**11%**

a Assumes U.S. approval in 1989. b Not meaningful. c Not now approved in U.S. **Source:** Sanford C. Bernstein & Co.

Perhaps the best-known rheumatoid disease that NSAIDs are designed to treat is rheumatoid arthritis. About 2.1 million Americans are afflicted, according to the Arthritis Foundation in Atlanta. Of these, about 1.5 million are women and 600,000 men.

The disease can be difficult to diagnose. Osteoarthritis, which is nonrheumatoid, is more common, affecting about 16 million Americans. And such infectious diseases as gonorrhea and Lyme disease (infection by the spirochete *Borrelia burgdorferi*, transmitted by tick bites) cause their own forms of arthritis.

The Arthritis Foundation has published a scorecard of 11 criteria to aid diagnosis, including patterns of pain and joints involved, x-ray signs, and tests of blood, synovial (interi-

or joint) fluid, and joint tissues. Seven positive signs denote "classic" rheumatoid arthritis, whereas five mean "definite," three "probable," and two "possible."

One sign of the autoimmune nature of rheumatoid arthritis is so-called rheumatoid factor in blood. Rheumatoid factor is antibody, usually of the immunoglobulin M (IgM) type, that reacts with human IgG. About 75% of rheumatoid arthritis patients have rheumatoid factor, though 5 to 10% of persons over age 60 also have it.

Also, large numbers of rheumatoid arthritis patients have a human leukocyte antigen (HLA) called DR4. HLAs are proteins embedded in outer surfaces of almost every human cell. Their pattern of occurrence is individual to each person and guides the immune system in distinguishing between cells, particles, and proteins that are "self" and "nonself." HLAs are coded for by a set of genes on chromosome 6 called the major histocompatability locus.

During routine immune surveillance, blood cells called polymorphonuclear (PMN) leukocytes ingest various proteins, particles, or other cells they find, degrade these internally, and present the products on their own surfaces. The PMNs then secrete interleukin-1, which activates other blood cells called T-cells to interact with these new antigens and the HLAs normally present to test for self versus nonself.

If the result is nonself, the T-cell secretes interleukin-2, which stimulates growth of other T-cells sensitive to that antigen. The T-cell also presents the antigen to other blood cells called B-cells and secretes interleukin-4 and a substance called B-cell differentiation factor. Interleukin-4 stimulates growth of B-cells sensitive to the antigen. The differentiation factor induces B-cells to produce antibodies against it.

Interleukin-1 has other widespread influences that include release of prostaglandins and potently oxidizing superoxide (O_2^{1-}) ions as well as destruction of bone and cartilage. This underscores the importance of finding drugs that inhibit production of interleukin-1 during inappropriate immune reactions against the body's own tissue.

Joint destruction of rheumatoid arthritis occurs at different rates in different patients. Thus doctors can manage from 50 to 75% of such patients on NSAIDs as sole drug therapy.

Physical and occupational therapy help to keep joints mobile and strengthen associated muscles. Proper balance of muscle contracture avoids deformation of joints. Psychological counseling may also be needed, as well as complete bed rest during severe flares of disease.

For patients in which NSAIDs do not arrest joint destruction, doctors must add "slow acting" or "disease-modifying" drugs. These include

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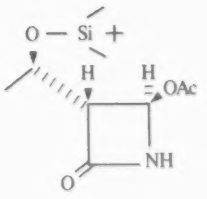
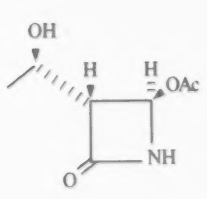
PENEMS & CARBAPENEMS



(3R, 4R)-4-Acetoxy-3-[(R)-(tert-butyldimethylsilyloxy) ethyl]-2-azetidinone (AZETIDON-KANEKA)



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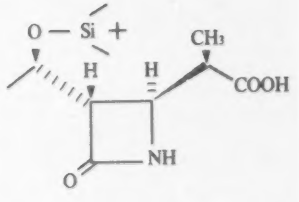

(3S, 4S)-3-[(R)-(tert-Butyldimethylsilyloxy) ethyl]-4-[(R)-carboxyethyl]-2-azetidinone

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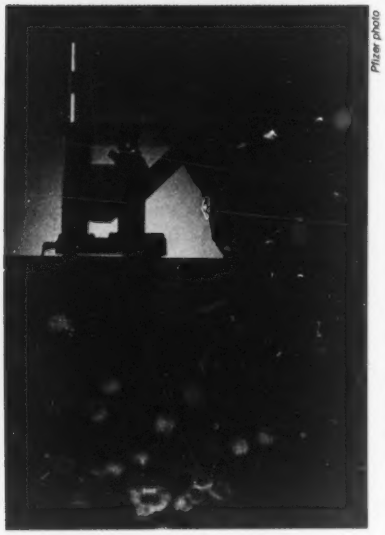

Pfizer photo

Researcher uses electron micrograph to study inflammatory cells produced in arthritic joint disease

gold salts, penicillamine, antimalarials, cytotoxic agents, and immunosuppressants. The way in which these drugs arrest the rheumatoid process is mostly unknown, and patients must take them for four to nine months to see if they can be tolerated or if they work at all. Analyst Habermas predicts that doctors will move more aggressively in the future to prescribe such drugs.

Gold salts include injectable gold sodium thiomalate and gold thioglucose. SmithKline Beecham has recently received FDA approval to market Ridaura brand of auranofin, an acetylated gold thioglucose, which has the advantage of being an oral drug with lower incidence of side effects, but which also may be less effective than the injectables.

If gold fails, doctors can turn to penicillamine or the antimalarials chloroquine or hydroxychloroquine. Also available are the cytotoxic drugs cyclophosphamide and methotrexate. Lederle Laboratories, Pearl River, N.Y., introduced Rheumatrex, an oral form of methotrexate for rheumatoid arthritis last January.

Patients take only 7.5 mg of Rheumatrex once weekly. This contrasts with the 20- to 12,000-mg daily doses given as cancer chemotherapy. Because of the unusual antiarthritic dosage of one 2.5-mg tablet three times in the 24-hours of one single day a week, Lederle has packaged the tablets in special blister packs of three. This packaging, together with the doctor's instructions, helps patients keep to this rigid pattern.

Medicinal chemists also have given attention to such immunosuppressant drugs as cyclosporin A and FK-506. Both compounds are macrocycles, but cyclosporin A is a polypeptide and FK-506 is a lactonelactam. Though cyclosporin A is an established drug used thus far to suppress rejection of transplanted organs, there is even greater interest in FK-506, because it is 100 times more powerful. FK-506 was discovered at Fujisawa Pharmaceutical Co. in Japan, and its total synthesis has been achieved by chemists at Merck, Rahway, N.J. (C&EN, Feb. 6, page 29).

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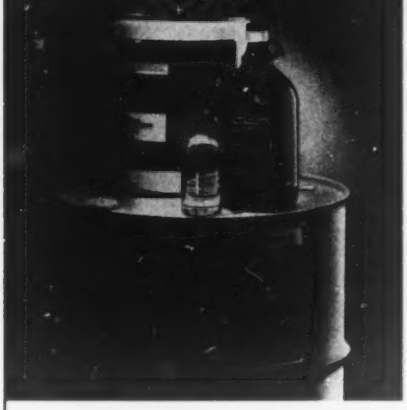

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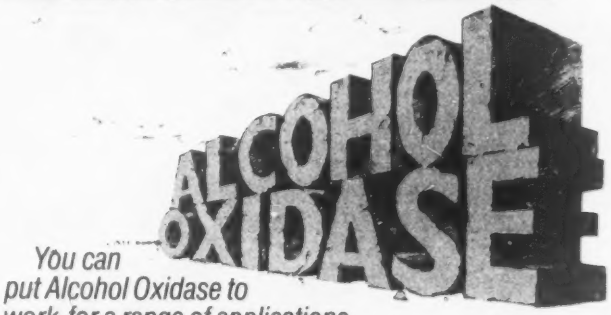

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Product Report

Michael J. Schmidt of Merck notes that cyclosporin A dramatically shuts down production of interleukin-2 and has been effective in treating rheumatoid arthritis. The compound damages patients' kidneys in long-term therapy, however, and any agent for rheumatoid arthritis must be safe in chronic dosages.

FK-506 stops production of interleukin-2 and -4 as well as another immunologic substance called interferon-γ, apparently by preventing syntheses of messenger ribonucleic acids (mRNAs) for those proteins. But FK-506 is also toxic to kidneys.

Now that total synthesis of FK-506 is complete, however, Merck chemists can make analogs that may have the immunosuppressant effect but lack the toxicity. Success hinges on whether toxicity is mechanism-based or idiosyncratic, Schmidt says. If mechanism-based, then the whole class of drugs will be toxic by their very mode of action, and the outlook is dim. But if it is unique to one compound, there is hope of developing a successful agent.

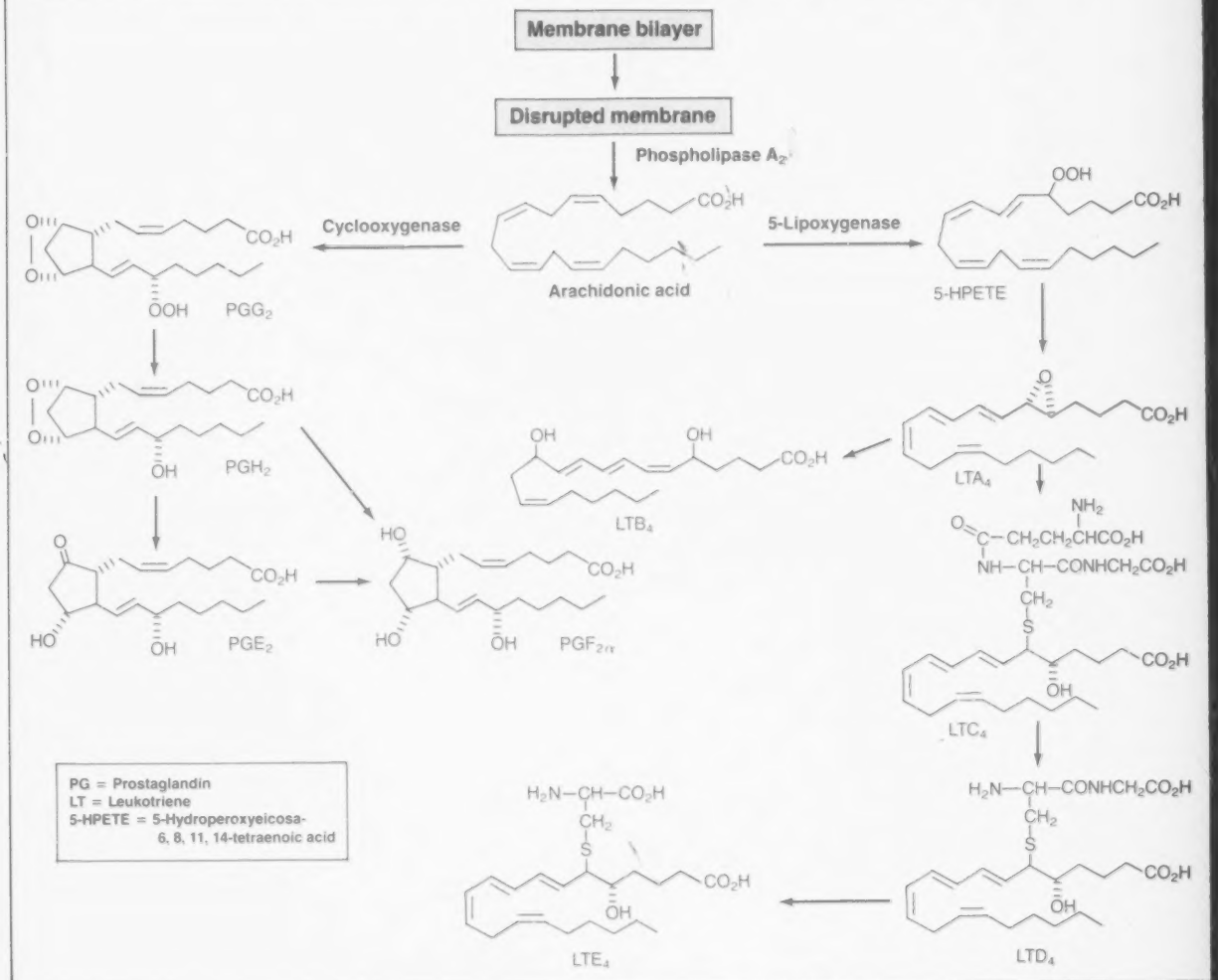
Two diseases related to rheumatoid arthritis are juvenile rheumatoid arthritis and ankylosing spondylitis (intervertebral inflammation that causes fusion of vertebrae).

Juvenile rheumatoid arthritis is actually three or more diseases, classified according to whether they affect few joints, many joints, or have systemic effects throughout the body. The Arthritis Foundation estimates that about 71,000 children under age 16 are afflicted, 61,000 of them girls.

Treatment is the same as for rheumatoid arthritis, relying on NSAIDs, physical therapy, and education, and going on to disease-modifying drugs if necessary. There is special concern to avoid joint deformity and ensure normal growth, because patients are growing children. For this reason, oral steroids are not given long-term, though steroid injections directly into joints may help severe disease. Doctors are divided on whether gold salts are truly effective in the juvenile diseases.

Many juvenile arthritis patients and 90% of those with ankylosing spondylitis have HLA B27. But 5 to 10% of normal persons also have this antigen, which points up the

Cascade of reactions of arachidonic acid produces mediators of inflammation



lack of fundamental understanding of rheumatoid disease.

In spite of its name, ankylosing spondylitis can also affect large joints and cause anterior uveitis, which is an inflammation of the iris of the eye. The Arthritis Foundation estimates that 318,000 Americans have ankylosing spondylitis, of whom 229,000 are men. Treatment includes NSAIDs, but the slow acting, disease-modifying drugs seem ineffective.

Though not a rheumatoid disease, osteoarthritis, also called degenerative joint disease, is a widespread, devastating condition that is treated similarly. The Arthritis Foundation estimates that 15.8 million Americans suffer from osteoarthritis, of whom 11.7 million are women.

Osteoarthritis involves destruction of cartilage and excess bone growth at joints, apparently from processes intended to repair normal wear and tear. Slight signs of it can appear between ages 10 and 30, and almost all persons have such joint changes by age 70. Occurrence of osteoarthritis as a disease depends on how fast the process works in individuals and whether pain and joint stiffening appear. The much greater incidence in women than in men leads many doctors to think that steroid hormones may be involved.

Cartilage consists of a matrix of glycoprotein fibers containing cells called chondrocytes. Chondrocytes multiply and synthesize matrix proteins and sugars in response to minute injuries or repetitive impact.

Because cartilage lacks blood vessels, it depends on nutrients from synovial (interior joint) fluid on one side and bone on the other. Compression of the joint squeezes fluid containing metabolic wastes out of cartilage, which is 70% water, into synovial fluid. Release of compression allows reabsorption of nutrient-containing fluid.

The aging process, whatever that may be, causes cartilage to lose this resilience. Minute injuries can result in release of prostaglandins and interleukin-1 into the joint. Among

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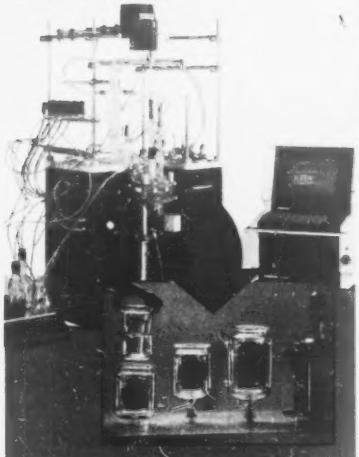

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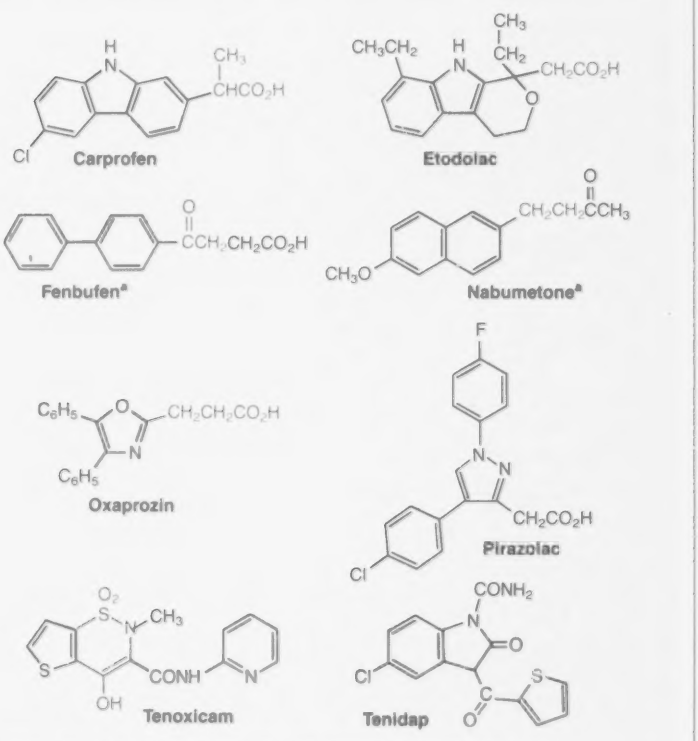
New anti-inflammatory drugs await U.S. approval



Note: Groups of atoms in color are those that make each compound a member of its class.
a Active metabolite is RCH_2CO_2H.

other things, interleukin-1 can stimulate production of cartilage-destroying enzymes.

As cartilage degrades, bone tissue grows in a density greater than normal at the bone ends. Some new bone growth occurs as sharp spurs. The denser, stiffer, new bone is susceptible to microfractures with constant use of the joint. These microfractures can stimulate more bone growth and cartilage destruction.

In x-rays, doctors can see dense new bone, appearance of spurs and microfractures, and a narrowing of the space between bone ends. Treatment includes the same physical therapy and NSAIDs as for rheumatoid arthritis. In addition, such muscle relaxants as high-dose diazepam may be needed to ease pain of muscles that lock in a stiffened state in response to joint damage.

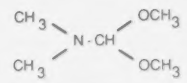
A rheumatoid disease that can affect any or all tissues of the body is systemic lupus erythematosus (SLE, "red wolf disease"). This disease takes its name from a red rash that sometimes forms on patients' cheeks and that, in some, gives the face a wolflike appearance. Though most SLE patients develop rashes of some sort and have abnormally photosensitive skin, the classic "butterfly" rash appears in fewer than half.

Based on findings of some epidemiologists, the Arthritis Foundation has estimated that there are 131,000 SLE patients in the U.S., 117,000 of them women. But spokesmen for the American Lupus Society in Torrance, Calif., say that a more likely number is 200,000. There is agreement that about 90% of SLE patients are women, and that greater numbers of black women are afflicted than white.

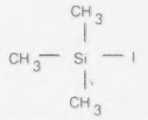
Symptoms vary widely, and SLE can mimic many other diseases. Some symptoms seem nonspecific,

DAVOS

N,N-Dimethylformamide Dimethyl Acetal



Trimethyl Silyl Iodide



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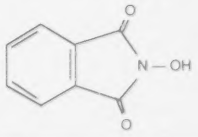
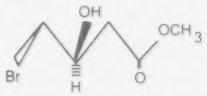
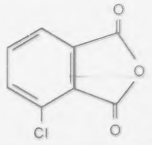


Methyl-(S)-(-)-4-Bromo-3-Hydroxybutanoate



(1S, 2R, 4R)-endo-Norborneol

3-Chloro Phthalic Anhydride



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such as chronic fatigue, fever that comes and goes, joint pain, swollen glands and/or spleen, and a general feeling of being unwell. The disease flares and goes into remission. Patients often recognize onset of chronic fatigue as a warning sign of a new flare.

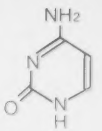
Other symptoms can be more dramatic but no less baffling, such as psychotic episodes and seizures resembling grand mal epilepsy. And the kidney is very susceptible to attack. Though early diagnosis and improved treatment have raised 10-year survival rates to about 90%, half of all deaths of SLE patients are from kidney disease.

With SLE as in rheumatoid arthritis, doctors usually depend on a scorecard of 11 criteria developed by physician Eng M. Tan at Scripps Clinic & Research Foundation, La Jolla, Calif. These are the butterfly rash, discoid (plaquelike) rash on other parts of the body, rash from overexposure to sunlight, ulcers in the mouth, arthritis in two or more joints, inflammation of tissue sacs around the heart (pericarditis) or lungs (pleuritis), protein or blood cell debris in urine, seizures or psychosis, low counts of certain blood cell types, antibodies to human cell nuclei, and any of certain other immunologic abnormalities. Doctors can diagnose SLE if any four of these symptoms are present.

Treatment is similar to that of rheumatoid arthritis, but tailored to individual cases. NSAIDs are effective against fever, joint pain, pericarditis, and pleuritis. Mouth ulcers and the various types of rashes may respond to chloroquine or hydroxychloroquine. Acute attacks of kidney disease, anemias involving various blood cell types, or psychiatric symptoms require high doses of oral or injected steroids like prednisone or methylprednisolone. These acute symptoms have also been treated with azathioprine, cyclophosphamide, and methotrexate, with and without steroids.

Pregnancy is a difficult problem for many female SLE patients. Miscarriages occur in about 25% of attempts, perhaps owing to blood clots in the placenta. And hormonal changes may cause severe flares in weeks following delivery. □

INTERMEDIATES FOR PHARMACEUTICALS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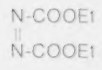
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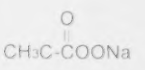
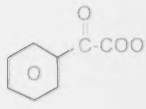

SODIUM PYRUVATE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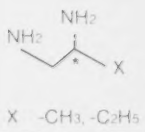
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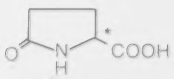
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